

We claim:

1. A transgenic non-human mammal, the germ cells and somatic cells of which contain an inactivated HMGI gene sequence introduced into the mammal, or an ancestor of the mammal, at an embryonic stage.

2. The mammal according to claim 1, wherein the inactivated HMGI gene sequence is an inactivated HMGI-C gene sequence.

3. The mammal according to claim 2, wherein the inactivated HMGI-C gene sequence is the sequence of the mutant HMGI-C gene set out in Figure 10.

4. The mammal according to claim 1, wherein the mammal is a rodent.

5. The mammal according to claim 4, wherein the rodent is a mouse.

6. A method for treating obesity in a mammal which comprises reducing the biological activity of HMGI genes in the mammal.

7. The method according to claim 6, wherein at least 10% of the biological activity of HMGI genes is reduced.

8. The method according to claim 7, wherein at least 25% of the biological activity of HMGI genes is reduced.

9. The method according to claim 8, wherein at least 50% of the biological activity of HMGI genes is reduced.

10. The method according to claim 6, wherein the biological activity of HMGI-C genes is reduced.

0865266-050797

20  
sub  
21

11. The method according to claim 6, wherein the mammal is leptin-deficient or leptin receptor-deficient.

12. The method according to claim 6, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the expression of HMGI genes.

13. The method according to claim 12, wherein inhibition of the expression of HMGI genes is achieved by administering to the mammal a therapeutically effective amount of an oligonucleotide which has a nucleotide sequence complementary to at least a portion of the mRNA of the HMGI gene.

14. The method according to claim 6, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the DNA-binding activity of HMGI genes.

15. The method according to claim 14, wherein the inhibition of the DNA-binding activity of HMGI genes is achieved by administering to the mammal a therapeutically effective amount of netropsin, distamycin A, or Hoechst 33258 (bisbenzimidazole).

16. The method according to claim 6, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the protein-protein interactions of HMGI proteins.

17. The method according to claim 6, wherein the mammal is a human.

18. The method according to claim 6, wherein the mammal is a rodent.

19. The method according to claim 18, wherein the rodent is a mouse.

0852666.050797

20. The method according to claim 18, wherein the biological activity of HMGI is substantially reduced by breeding the mammal with an inactivated HMGI gene sequence introduced into the mammal, or an ancestor of the mammal, at an embryonic stage.

21. The method according to claim 20, wherein the inactivated HMGI gene sequence is an inactivated HMGI-C gene sequence.

22. The method according to claim 21, wherein the inactivated HMGI-C gene sequence is the sequence of the mutant HMGI-C gene set out in Figure 10.

23. A method for regulating growth and development of adipose tissue in a mammal which comprises reducing the biological activity of HMGI genes in the mammal.

24. The method according to claim 23, wherein the mammal is leptin-deficient or leptin receptor-deficient.

25. The method according to claim 23, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the expression of HMGI genes.

26. The method according to claim 25, wherein inhibition of the expression of HMGI genes is achieved by administering to the mammal a therapeutically effective amount of an oligonucleotide which has a nucleotide sequence complementary to at least a portion of the mRNA of the HMGI gene.

27. The method according to claim 23, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the DNA-binding activity of HMGI genes.

28. The method according to claim 27, wherein the inhibition of the DNA-binding activity of HMGI genes is achieved by administering to the mammal

05025555.050797

a therapeutically effective amount of netropsin, distamycin A, or Hoechst 33258 (bisbenzimidazole).

29. The method according to claim 23, wherein the reduction in biological activity of HMGI genes is achieved by inhibiting the protein-protein interactions of HMGI proteins.

30. The method according to claim 23, wherein at least 10% of the biological activity of HMGI genes is reduced.

31. The method according to claim 30, wherein at least 25% of the biological activity of HMGI genes is reduced.

32. The method according to claim 31, wherein at least 50% of the biological activity of HMGI genes is reduced.

33. A method for screening candidate compounds capable of inhibiting HMGI biological activity which comprises the steps of:

(a) immobilizing a HMGI protein or a fragment thereof on a solid surface;

(b) incubating the HMGI protein with a candidate compound under conditions which promote optimal interaction; and

(c) measuring the binding affinity of the candidate compound to the HMGI protein or a fragment thereof; and

(d) determining from the binding affinity which candidate compounds inhibit the HMGI biological activity.

34. The method according to claim 33, wherein the candidate compound inhibits HMGI biological activity in an amount of at least 10%.

35. The method according to claim 34, wherein the candidate compound inhibits HMGI biological activity in an amount of at least 25%.

36. A method for screening candidate compounds capable of inhibiting HMGI biological activity which comprises the steps of:

- (a) transfecting into a cell a DNA construct which contains a reporter gene under control of an HMGI protein-regulated promoter;  
(b) administering to the cell a candidate compound;  
(c) measuring the levels of reporter gene expression; and  
5 (d) determining from the levels of reporter gene expression which candidate compounds inhibit the HMGI biological activity.

37. The method according to claim 36, wherein the candidate compound inhibits HMGI biological activity in an amount of at least 10%.

10 38. The method according to claim 37, wherein the candidate compound inhibits HMGI biological activity in an amount of at least 25%.

15 39. A mammal whose genome does not encode for both the functionally active leptin gene and the functionally active HMGI genes.

40. The mammal according to claim 39, wherein the HMGI gene is the HMGI-C gene.

08852666.0509  
"64050" 99925880

add C1  
add D1  
add E1  
add F1  
add G1